Critical Care

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Feasibility and safety of ultra-low volume ventilation (≤ 3 ml/kg) combined with extra corporeal carbon dioxide removal ($ECCO_2R$) in acute respiratory failure patients

Clément Monet[1,2], Thomas Renault[1], Yassir Aarab[1,2], Joris Pensier[1,2], Albert Prades[1], Ines Lakbar[1,2], Clément Le Bihan[1], Mathieu Capdevila[1,2], Audrey De Jong[1,2*], Nicolas Molinari[3,4] and Samir Jaber[1,2*]

Abstract

Background Ultra-protective ventilation is the combination of low airway pressures and tidal volume (Vt) combined with extra corporeal carbon dioxide removal ($ECCO_2R$). A recent large study showed no benefit of ultra-protective ventilation compared to standard ventilation in ARDS (Acute Respiratory Distress Syndrome) patients. However, the reduction in Vt failed to achieve the objective of less than or equal to 3 ml/kg predicted body weight (PBW). The main objective of our study was to assess the feasibility of the ultra-low volume ventilation (Vt ≤ 3 ml/kg PBW) facilitated by $ECCO_2R$ in acute respiratory failure patients.

Methods Retrospective analysis of a prospective cohort of patients with either high or low blood flow veno-venous $ECCO_2R$ devices. A session was defined as a treatment of $ECCO_2R$ from the start to the removal of the device (one patient could have one more than one session). Primary endpoint was the proportion of sessions during which a Vt less or equal to 3 ml/kg PBW at 24 h after the start of $ECCO_2R$ was successfully achieved for at least 12 h. Secondary endpoints were respiratory variables, rate of adverse events and outcomes.

Results Forty-five $ECCO_2R$ sessions were recorded among 41 patients. Ultra-low volume ventilation (tidal volume ≤ 3 ml/kg PBW, success group) was successfully achieved at 24 h in 40.0% sessions (18 out of 45 sessions, confidence interval 25.3–54.6%). At 24 h, tidal volume in the failure group was 4.1 [3.8–4.5] ml/kg PBW compared to 2.1 [1.9–2.5] in the success group ($p < 0.001$). After multivariate analysis, blood flow rate was significantly associated with success of ultra-low volume ventilation (adjusted OR per 100 ml/min increase 1.51 (95%CI 1.21–1.90, $p = 0.0003$).

Conclusion Ultra-low volume ventilation (≤ 3 ml/kg PBW) was feasible in 18 out of 45 sessions. Higher blood flow rates were associated with the success of ultra-low volume ventilation.

Keywords Extracorporeal carbon dioxide removal, ECCO2R, Acute respiratory distress syndrome, Intensive care, Ventilator-induced lung injury

*Correspondence:
Audrey De Jong
a-de_jong@chu-montpellier.fr
Samir Jaber
s-jaber@chu-montpellier.fr
Full list of author information is available at the end of the article

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Take-home message

In a cohort of 41 patients treated with ECCO2R, ultra-low volume ventilation (tidal volume ≤ 3 ml/kg of predicted body weight) was feasible for at least 12 h with a success rate of 40.0% (confidence interval 25.3–54.6%). Higher blood flow rates were associated with the success of ultra-low volume ventilation.

140-character tweet

Ultra-low volume ventilation (tidal volume ≤ 3 ml/kg) is feasible with ECCO2R when using higher blood flow rates.

Background

Acute respiratory failure is the leading cause of Intensive Care Unit (ICU) admission and remains associated with high mortality, especially in patients requiring invasive mechanical ventilation [1, 2]. Although necessary, invasive ventilation can contribute to pulmonary injury and inflammation, commonly referred to as «ventilator-induced lung injury» (VILI) [3]. Different mechanisms can be implicated: barotrauma, volutrauma, atelectrauma and biotrauma [4, 5]. Protective ventilation strategies (low tidal volume (Vt) of 4–8 ml/kg of predicted body weight (PBW) and plateau pressure (Pplat) lower than 30 cmH_2O [6]) have proven to limit VILI and improve outcomes in ARDS (Acute Respiratory Distress Syndrome) patients and in ventilated patients without underlying lung injury [6, 7]. However, in some ARDS patients treated with protective ventilation strategy, hyperinflation and lung injury could still occur when lung protective ventilation targets are not met [8, 9]. These patients could justify and benefit from a better control of Vt and Pplat [10, 11]. The limiting factor of this strategy is the carbon dioxide accumulation and respiratory acidosis. Extra corporeal carbon dioxide removal ($ECCO_2R$) addresses this issue by removing carbon dioxide via an extracorporeal circuit and maintaining pH and $PaCO_2$ within physiological range values [12]. This combination has been described as "ultra-protective ventilation" [12, 13]. However, the lack of high-quality data and the high heterogeneity in devices and practices made it difficult to conclude on efficacy regarding patient-centered outcomes and $ECCO_2R$ might even be detrimental [14, 15]. Recently, a large randomized controlled trial showed no benefit of ultra-protective ventilation compared to standard ventilation in ARDS patients [16]. However, in this study the reduction in Vt failed to achieve the objective of "less than or equal to 3 ml/kg PBW" and ultraprotective ventilation was only maintained for a short period of time. We made the hypothesis that difficulties to achieve ultra-low volume ventilation (Vt ≤ 3 ml/kg PBW) could be explained by insufficient CO_2 removal. The main objective of this study was to assess the feasibility of ultra-low volume ventilation (Vt ≤ 3 ml/kg PBW) in acute respiratory failure patients. Secondary objectives were to evaluate efficacy and safety of ultra-low volume ventilation as well as to identify factors associated with the feasibility of ultra-low volume ventilation.

Methods

Patients and ethics

We conducted a retrospective, pragmatic, descriptive analysis of a cohort of patients who consecutively underwent $ECCO_2R$ treatment in a single French center. All patients admitted from June 2014 to December 2022, who presented an acute respiratory failure and were treated with $ECCO_2R$ therapy at any point during their ICU stay were included. The Institutional Review Board of Montpellier University Hospital approved the study (2019_IRB-MTP_05-25).

Collected data

Demographic characteristics (age, gender, body mass index), comorbidities and severity scores (Simplified Acute Physiology Score II, SAPS II, and the Sequential Organ Failure Assessment, SOFA[17, 18]) were collected at admission. Respiratory variables (tidal volume, plateau pressure, positive end-expiratory pressure, driving pressure, minute ventilation) and gas exchanges (PaO_2/FIO_2 ratio, $PaCO_2$, pH) were prospectively collected at the start of $ECCO_2R$ (H0) and 4, 24 and 48 h after initiation of $ECCO_2R$ (referred in this study as H0, H4, H24, H48). Mechanical power was calculated using the simplified formula described by Gattinoni et al. [19]. $ECCO_2R$ technical characteristics were also recorded: cannula type and size, blood flow rates, and anticoagulation methods. Ventilatory ratio (VR), which is a composite variable reflective of dead space and shunt, was computed as previously described [20] (see Supplementary appendix). $ECCO_2R$-related adverse events ($ECCO_2R$-AE) were recorded and classified as mechanical and clinical [21] (complete definitions are provided in the Supplementary appendix). Indication and duration of $ECCO_2R$, adjunctive ARDS treatments, time from intubation to $ECCO_2R$, duration of invasive mechanical ventilation, duration of ICU stay, and 90-day survival were also recorded.

$ECCO_2R$ treatment

Extra corporeal carbon dioxide removal treatment was performed with 4 different veno-venous devices: Hemolung Respiratory Assist System® (ALung Technologies, Pittsburgh, USA); iLA activve® (Xenios, Fresenius medical care company, Germany), Prismalung® and Prismalung + ® (Baxter Healthcare, Sweden). A percutaneous venous access was obtained. The femoral or jugular vein

was catheterized at physicians' discretion. Devices were classified as: low blood flow $ECCO_2R$ devices (blood flow less than 500 ml/min) and high blood flow $ECCO_2R$ devices (blood flow greater than or equal to 1000 ml/min). Low blood flow $ECCO_2R$ devices were: (1) Prismalung® which is a gas exchanger for CO_2 removal on the Prismaflex system with a $0.32m^2$ heparin coated polymethylpentene (PMP) membrane (2) Prismalung + ® with a $0.8m^2$ phosphorylcholine coated PMP membrane (3) Hemolung Respiratory Assist System® with a $0.59m^2$ siloxane and heparin coated hollow fibers membrane. The high blood flow $ECCO_2R$ device was the iLA activve® with a heparin coated $1.3m^2$ PMP hollow fiber membrane. Anticoagulation was left to the clinician discretion based on coagulation test, manufacturer instructions and clinical data.

Protocol of the study

The $ECCO_2R$ initiation protocol was as follows: the targeted blood flow was the maximum blood flow according to available data and/or manufacturer (for the high blood flow $ECCO_2R$ devices, we arbitrarily limited the blood flow to 2000 ml/min). When the targeted blood flow (or maximum achievable blood flow) was reached, sweep gas flow was increased from 0 L/min to 10 L/min with 2 L/min steps every 30 min. Simultaneously Vt was decreased every 30 min by 0.5 ml/kg with an objective of Vt ≤ 3 ml/kg PBW. Vt reduction was stopped when the patient developed signs of poor tolerance defined as follows: (1) $PaCO_2$ increasing more than 20% from the start of $ECCO_2R$ with a value of pH < 7.3, as previously described [21]; (2) discontinuation of $ECCO_2R$ therapy due to mechanical complication (membrane clotting, pump malfunction, etc.); (3) discontinuation of $ECCO_2R$ therapy due to clinical complication (hypoxemia, hemolysis, bleeding, etc.).

Endpoints

The primary endpoint was the proportion of sessions during which a Vt ≤ 3 ml/kg PBW was successfully achieved at 24 h after the start of $ECCO_2R$. We defined "$ECCO_2R$ session" as a treatment with $ECCO_2R$ from the start to the removal of the device, one patient could have one or more if treated again with $ECCO_2R$ for a new indication (same or different ICU stay). If a circuit change was necessary during a session, we still considered it as a single session. We then defined two groups: *(1)* the "success group" and *(2)* the "failure group" based on whether the endpoint was reached. Secondary endpoints included: duration of $ECCO_2R$, respiratory variables, ventilatory settings at H0, H4, H24 and H48, $ECCO_2R$-related adverse events and 90-day survival.

Statistical analysis

First, a descriptive analysis was performed overall, in the success group and in the failure group. For continuous data, the Gaussian distribution was checked using Shapiro–Wilk or Kolmogorov–Smirnov tests. Quantitative variables were expressed as mean (± standard deviation (SD)) or as median with interquartile ranges [IQR] (Gaussian or non-Gaussian variables) and compared using the Student t test or Mann–Whitney test respectively. Paired quantitative variables were compared using a paired Student t-test or Wilcoxon signed-rank test when appropriate (Gaussian or non-Gaussian variables). Qualitative variables were expressed as numbers (%) and compared using the chi-square test or Fisher's exact test, as appropriate (when expected frequencies were less than five). Paired qualitative variables were compared with a McNemar test. Then, a multivariate logistic regression model was performed to provide adjusted results of success of ultra-low volume ventilation (primary outcome), considering a priori the variables age, body mass index, SAPS II, driving pressure and blood flow rate (per 100 ml/min increase). These factors were entered into the multivariate model, and a final model including only significant variables was computed. Adjusted odds ratio (OR) with 95% confidence intervals (CI) were computed. Statistical significance was considered at $p < 0.05$; p values were two-tailed. All analyses were done with the use of SAS Enterprise Guide (version 7.13) or statistical software R (version 4.0.3; R Foundation for Statistical Computing). Regarding 90-day survival, patients who had more than one session were analyzed in the group corresponding to the first session.

Results

Sessions characteristics

We report 45 sessions of $ECCO_2R$ in our unit from June 2014 to December 2022 among 41 patients. Among the 45 sessions: 18 sessions were included in the success group (≤ 3 ml/kg PBW) and 27 sessions in the failure group (> 3 ml/kg PBW). One patient was included in both groups (1 session in each group). Sessions characteristics can be found in Table 1. Demographics did not significantly differ between the two groups. SOFA and SAPS II score were high without significant difference between groups (10 [6–13] vs. 10 [7–15] $p = 0.49$ and 54 [40–58] vs. 47 [34–65] $p = 0.83$, respectively) (Table 1). Indication for $ECCO_2R$ in the overall population was ARDS for 37 (82%) sessions without a significant difference between groups. Respiratory variables and ventilatory settings before the start of $ECCO_2R$ were not significantly different between the two groups, except for driving pressure (14.0 [10.3–18.8] cmH_2O in the failure group versus

Table 1 Overall sessions characteristics at baseline and comparison between the failure group and the success group

Sessions characteristics	Overall sessions (n = 45)	Failure group (n = 27)	Success group (n = 18)	p value
Age, years	60 [48–65]	60 [52–63]	57 [41–66]	0.93
Female gender	13 (29)	9 (33)	4 (22)	0.42
Size, cm	172 [165–176]	170 [165–175]	174 [170–176]	0.13
Weight, kg	80 [69–84]	80 [70–85]	75 [63–84]	0.32
Body mass index, kg/m^2	27 [23–28]	27 [24–29.5]	25 [20–28]	0.21
Reason for ICU admission				
Medical	26 (58)	13 (48)	13 (72)	0.11
Surgical	19 (42)	14 (52)	5 (28)	0.11
SAPS II	52 [36–62]	54 [40–58]	47 [34–65]	0.83
SOFA score	10 [7–13]	10 [6–13]	10 [7–15]	0.49
Indication for $ECCO_2R$				
ARDS (Pulmonary/non-pulmonary)	37 (82)	22 (82)	15 (83)	0.99
Pulmonary	31 (69)	16 (59)	15 (83)	0.11
Pneumonia	9 (20)	5 (19)	4 (22)	0.99
Aspiration	7 (16)	2 (7)	5 (28)	0.1
Influenzae	2 (4)	1 (4)	1 (6)	0.99
Pulmonary complications of surgery	7 (16)	5 (19)	2 (11)	0.68
SARS-CoV-2 pneumonia	5 (11)	3 (11)	2 (11)	0.99
Antisynthetase syndrome	1 (2)	0 (0)	1 (6)	0.4
Non-pulmonary	6 (13)	6 (22)	0	0.07
SIRS/Sepsis	2 (4)	2 (7)	0	0.51
Transfusion Related Acute Lung Injury	4 (9)	4 (15)	0	0.14
Non-ARDS	8 (18)	5 (19)	3 (17)	0.99
Ultra-protective ventilation	3 (7)	2 (7)	1 (6)	0.99
Pulmonary fibrosis	2 (4)	0 (0)	2 (11)	0.15
Hypercapnic respiratory failure	1 (2)	1 (4)	0 (0)	0.99
Weaning failure	2 (4)	2 (7)	0 (0)	0.51
Time from intubation to $ECCO_2R$ initiation (days)	2 [1–6]	2 [1–4]	4 [1–9]	0.27

Values given as number (%) or median [Interquartile range]

Success group: ≤ 3 ml/kg of predicted body weight), Failure group: > 3 ml/kg of predicted body weight, $ECCO_2R$: extracorporeal carbon dioxide removal, SOFA: Sepsis-related Organ Failure Assessment, SAPS: simplified acute physiology score, ARDS: acute respiratory distress syndrome, ICU: intensive care unit, SIRS: systemic inflammatory response syndrome

20.0 [16.3–22.8] cmH_2O in the success group, $p = 0.018$) (Table 2). Adjunctive ARDS treatments prior to $ECCO_2R$ were more frequently applied in the success group (61.1% vs 29.6%, $p = 0.036$).

Technical characteristics of extracorporeal CO_2 removal

$ECCO_2R$ was maintained for 3 [1–4] days. The Prismalung® device was used for 15 (33.3%) sessions, the Prismalung + ® for 8 (17.8%) sessions, the Hemolung® device was used for 2 (4.4%) sessions and the iLA activve® device was used for 20 (44.4%) sessions. Twenty-nine $ECCO_2R$ sessions (64.4%) were performed using anticoagulation with unfractionated heparin. Sixteen (35.6%) sessions were performed without anticoagulation. Cannula sizes and insertion sites can be found in Table 3.

Primary endpoint, success of ultra-low volume ventilation

The proportion of sessions during which a Vt ≤ 3 ml/kg PBW at 24 h after the start of $ECCO_2R$ was successfully achieved for at least 12 h was 40.0% (confidence interval 25.3–54.6%) (18 out of 45). High blood flow $ECCO_2R$ devices were used in 17 out of 18 sessions (94.4%) in the success group compared to 3 out of 27 sessions (11.1%) in the failure group ($p < 0.001$) (Table 2). After multivariate analysis, only blood flow rate was retained in the final model and was significantly associated with success of ultra-low volume ventilation (adjusted OR per 100 ml/min increase 1.51 (95%CI 1.21–1.90, $p = 0.0003$).

Table 2 Overall respiratory variables at the start of $ECCO_2R$, before ultraprotective ventilation, and comparison between the failure group and the success group

Sessions characteristics	Overall sessions (n = 45)	Failure group (n = 27)	Success group (n = 18)	p-value
V_T (ml/kg)	5.9 [5.5–6.0]	6.0 [5.7–6.0]	5.7 [4.9–6.0]	0.21
V_T (ml)	390 [350–420]	395 [340–420]	385 [360–410]	0.87
Respiratory rate (breaths/min)	26 [24–30]	26 [22–30]	26 [25–30]	0.94
V_E (L/min)	9.6 [8.1–11.8]	10.0 [8.2–12.1]	9.6 [8.3–11.5]	0.89
PEEP (cmH_2O)	10 [8–12]	10 [8–12]	10 [7–11]	0.23
Pplat (cmH_2O)	28 [22–31]	27 [21–29]	29 [24–33]	0.08
Driving pressure (cmH_2O)	17.0 [12.5–22.0]	14.0 [10.3–18.8]	20.0 [16.3–22.8]	**0.018**
Cstat,rs (ml/cmH_2O)	25 [17–31]	27 [20–36]	20 [17–26]	0.052
Mechanical power (J/min)	28 [24–36]	30 [24–37]	28 [25–36]	0.42
Ventilatory ratio	1.74 [1.47–2.28]	1.87 [1.48–2.37]	1.64 [1.40–2.21]	0.68
$PaCO_2$ (mmHg)	46 [39–56]	47 [39–55]	41 [39.3–59.8]	0.87
pH	7.33 [7.25–7.42]	7.32 [7.25–7.41]	7.33 [7.24–7.42]	0.72
FiO_2	0.70 [0.50–0.90]	0.65 [0.45–0.8]	0.80 [0.60–1.00]	0.11
PaO_2 (mmHg)	77 [63–101]	78 [71–98]	72 [63–103]	0.33
PaO_2/FiO_2	128 [90–178]	154 [99–187]	116 [74–161]	0.09
Mode of ventilation				
Mandatory	43 (95)	25 (93)	18 (100)	0.66
Spontaneous	2 (4)	2 (7)	0 (0)	0.66
Adjunctive ARDS treatments before $ECCO_2R$				
Two or more adjunctive treatments	19 (42)	8 (30)	11 (61)	**0.036**
Muscle paralysis	41 (91)	23 (85)	18 (100)	0.24
Prone position	17 (38)	8 (29)	9 (50)	0.29
Pulmonary vasodilator	7 (16)	1 (4)	6 (33)	**0.02**

All statistically significant (**p**-value < 0.05) results appear in bold

Values given as number (%) or median [Interquartile range]

Success group: ≤ 3 ml/kg of predicted body weight), Failure group: > 3 ml/kg of predicted body weight, Vt: tidal volume, V_E: minute ventilation, driving pressure = P_{PLAT} minus PEEP, PEEP: positive end-expiratory pressure, Pplat: end-inspiratory plateau pressure, $PaCO_2$: partial pressure of arterial CO_2, PaO_2/FiO_2: ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2), ARDS: Acute respiratory distress syndrome, $ECCO_2R$: extracorporeal carbon dioxide removal, Cstat,rs: static respiratory compliance (ml/cmH_2O) = tidal volume divided by Pplat minus PEEP

Secondary endpoints

Respiratory variables over time

In the overall cohort, Vt decreased during $ECCO_2R$ from 5.9 [5.5–6.0] ml/kg PBW at the start of $ECCO_2R$ (H0) to 3.5 [2.3–4.3] ml/kg PBW at 24 h ($p < 0.001$) (Supplementary Table 1). At 24 h, Vt in the failure group was 4.1 [3.8–4.5] ml/kg PBW compared to 2.1 [1.9–2.5] in the success group ($p < 0.001$) (Fig. 1A). At 24 h after the start of $ECCO_2R$, overall blood flow rates were 500 [400–1500] ml/min, 400 [350–450] ml/min in the failure group versus 1500 [1100–1500] ml/min in the success group ($p < 0.001$) (Fig. 1B). Decrease in driving pressure was significantly greater in the success group compared to the failure group: absolute reduction of 11.5 [9.0; 13.8] cmH_2O versus 5.0 [2.0; 8.5] cmH_2O ($p = 0.007$) (Fig. 1C and 1D). There was no difference in variation of Pplat between the two groups (Supplementary Fig. 1) but a significant difference in PEEP (at 24 h increase of 3.5 [0.5;4.8] cmH_2O in the success group compared to 0 [-2.0; 2.0] cmH_2O in the failure group, $p = 0.003$) (Fig. 1E, F, Supplemental Table 4). At 24 h, mechanical power in the failure group was 16 [15–22] J/min compared to 7 [6–10] in the success group ($p < 0.001$). Gas exchanges variations over time during $ECCO_2R$ are reported in Fig. 2. Overall, $PaCO_2$ and pH were stable throughout the procedure (46 [39–56] mmHg and 7.33 [7.25–7.42] respectively at baseline to 46 [40–54] mmHg and 7.34 [7.31–7.44] at 24 h). $PaCO_2$ and pH were not statistically different between the groups at 24 h while the respiratory rate was significantly lower in the success group than in the failure group (20 [18–25] breaths/min compared to 24 [21–26] breaths/min, $p = 0.039$). Evolution over time of respiratory variables in each group can be found in the Supplementary Tables 2 and 3. Additional analysis comparing type of intervention (low versus high blood flow) can be found in the Supplementary Fig. 2. Variation of tidal volume was correlated with variation of

Table 3 Overall respiratory variables and $ECCO_2R$ technical characteristics at 24 h after $ECCO_2R$ start and comparison between the failure group and the success group

Sessions characteristics	Overall sessions (n = 45)	Failure group (n = 27)	Success group (n = 18)	p-value
V_T (ml/kg)	3.5 [2.3–4.3]	4.1 [3.8–4.5]	2.1 [1.9–2.5]	**< 0.001**
V_T (ml)	220 [150–280]	280 [235–300]	150 [113–180]	**< 0.001**
Respiratory rate (breaths/min)	24 [21–26]	24 [21–26]	20 [18–25]	0.12
V_E (L/min)	4.8 [3.1–6.5]	6.2 [5.0–7.3]	3.0 [2.8–3.8]	**< 0.001**
PEEP (cmH_2O)	10 [8–14]	10 [8–12]	13 [9–15]	0.08
Pplat (cmH_2O)	20 [17–24]	20 [16–22]	22 [20–24]	0.08
Driving pressure (cmH_2O)	8 [6–12]	8 [7–12]	10 [5–13]	0.78
Cstat,rs (ml/cmH_2O)	30 [17–37]	34 [26–39]	18 [13–28]	**0.02**
Mechanical power (J/min)	12 [7–16]	16 [15–22]	7 [6–10]	**< 0.001**
Ventilatory ratio	0.93 [0.46–1.31]	1.31 [1.01–1.54]	0.46 [0.36–0.67]	**< 0.001**
$PaCO_2$ (mmHg)	46 [40–54]	50 [43–55]	46 [40–54]	0.25
pH	7.34 [7.31–7.44]	7.34 [7.26–7.46]	7.36 [7.33–7.41]	0.72
FiO_2	0.60 [0.45–0.80]	0.50 [0.40–0.75]	0.60 [0.50–0.80]	0.33
PaO_2 (mmHg)	71 [59–90]	82 [60–90]	67 [56–89]	0.44
PaO_2/FiO_2	134 [94–185]	142 [100–178]	119 [82–179]	0.23
$ECCO_2R$ cannulas sizes				
Double lumen 13 Fr cannula	11 (24)	11 (41)	0 (0)	**< 0.001**
Double lumen 15 Fr cannula	14 (31)	13 (48)	1 (6)	**0.003**
Double lumen 18 Fr cannula	1 (2)	1 (4)	0 (0)	0.99
Double lumen 24 Fr cannula	18 (40)	2 (7)	16 (89)	**< 0.001**
Two single lumen cannulas (19 Fr and 17 Fr)	1 (2)	0 (0)	1 (6)	0.99
$ECCO_2R$ cannulas insertion site				
Femoral vein	35 (78)	19 (70)	16 (89)	0.12
Internal jugular vein	9 (20)	8 (30)	1 (6)	0.12
Femoral and jugular	1 (2)	0 (0)	1 (6)	0.99
Type of $ECCO_2R$ device				
Low blood flow	25 (56)	24 (89)	1 (6)	**< 0.001**
High blood flow	20 (44)	3 (11)	17 (94)	**< 0.001**

All statistically significant (**p**-value < 0.05) results appear in bold

Values given as number (%) or median [Interquartile range]

Success group: ≤ 3 ml/kg of predicted body weight), Failure group: > 3 ml/kg of predicted body weight, Vt: tidal volume, V_E: minute ventilation, driving pressure = P_{PLAT} minus PEEP, PEEP: positive end-expiratory pressure, Pplat: end-inspiratory plateau pressure, $PaCO_2$: partial pressure of arterial CO_2, PaO_2/FiO_2: ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2), ARDS: Acute respiratory distress syndrome, $ECCO_2R$: extracorporeal carbon dioxide removal, Cstat,rs: static respiratory compliance (ml/cmH_2O) = tidal volume divided by Pplat minus PEEP, Fr: French, Low blood flow $ECCO_2R$ devices: blood flow rates inferior to 500 ml/min, high blood flow $ECCO_2R$ devices: blood flow rates superior to 1000 ml/min

driving pressure with high blood flow rates but not with low blood flow rates.

Safety

$ECCO_2R$-related adverse events are all reported in Table 4. Thrombocytopenia, recorded in 15 out of 45 sessions, was the most frequent adverse event, without significant difference between groups (44.4% in the success group versus 25.9% in the failure group, $p = 0.21$). No event of circuit or membrane coagulation was recorded in the success group versus 7 events (25.9%) in the failure group. One patient suffered from an intracerebral hematoma during $ECCO_2R$, he had severe coagulopathy unrelated to $ECCO_2R$ at the time.

Outcomes

Overall 90-day survival rate was 44% (18 out of 41 patients). The 90-day survival rate was 63% (15 out of 24 patients)) in the failure group versus 18% (3 out of 17 patients) in the success group ($p = 0.0004$). Overall

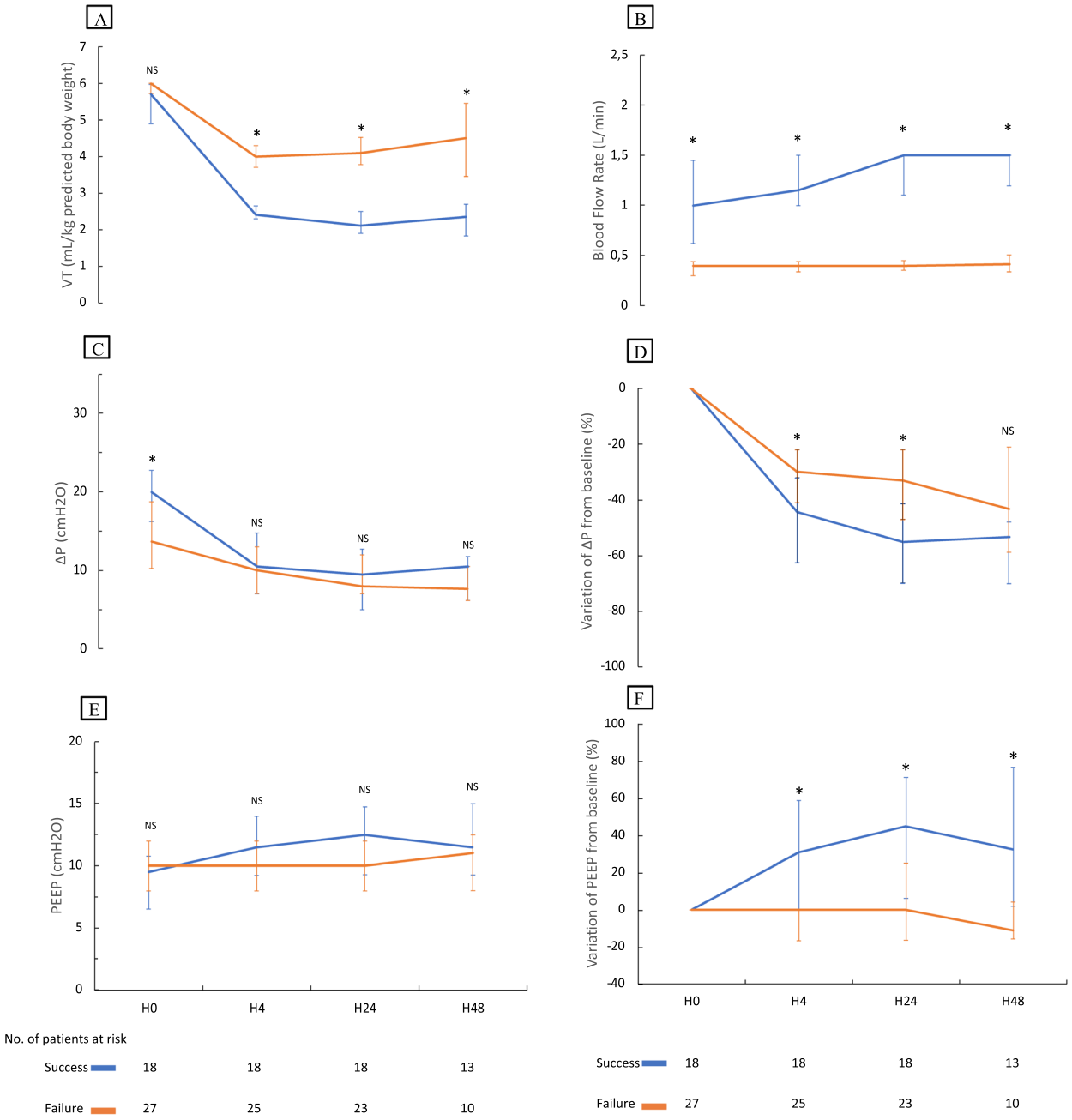

Fig. 1 Evolution over time of tidal volume, blood flow rate, driving pressure and positive end-expiratory pressure. Median, 1st and 3rd quartiles values of tidal volume (VT) (**A**), blood flow rate (**B**), driving pressure ($\Delta P = P_{PLAT}$ minus PEEP) (**C**) and PEEP (**E**) at the start of $ECCO_2R$ (H0), 4, 24, 48 h after initiation of $ECCO_2R$ in the failure group (> 3 ml/kg of predicted body weight) and in the success group (≤ 3 ml/kg of predicted body weight). Median, 1st and 3rd quartiles values of variation of driving pressure ($\Delta P = P_{PLAT}$ minus PEEP) (**D**), positive end-expiratory pressure (PEEP) (**F**) from the start of $ECCO_2R$ (H0) to 4, 24, 48 h after initiation of $ECCO_2R$ in the failure group (> 3 ml/kg of predicted body weight) and in the success group (≤ 3 ml/kg of predicted body weight). *$p < 0.05$ between groups, NS: not significant

duration of mechanical ventilation was 18 [9–30] days without significant difference between groups. Two patients were switched to extracorporeal membrane oxygenation (ECMO) because of worsening of PaO_2/FiO_2 ratio.

Table 4 ECCO2R-related adverse events

$ECCO_2R$-related adverse events	Overall sessions (n = 45)	Failure group (n = 27)	Success group (n = 18)	*p*-value
Mechanical				
Catheter-related				
Arterial insertion	1 (2)	0 (0)	1 (6)	0.40
Insertion difficulties	0 (0)	0 (0)	0 (0)	0.99
Accidental catheter removal	0 (0)	0 (0)	0 (0)	0.99
Device-related				
Pump malfunction	2 (4)	2 (7)	0 (0)	0.51
Membrane lung clotting	7 (16)	7 (26)	0 (0)	**0.031**
Cannula thrombosis	0 (0)	0 (0)	0 (0)	0.99
Air embolism	0 (0)	0 (0)	0 (0)	0.99
Tubing rupture	0 (0)	0 (0)	0 (0)	0.99
Clinical				
Hemolysis	3 (7)	1 (4)	2 (11)	0.55
Significant bleeding	2 (4)	0 (0)	2 (11)	0.15
Pneumothorax	0 (0)	0 (0)	0 (0)	0.99
Hemodynamic instability	7 (16)	4 (15)	3 (17)	0.99
Thromboembolic complications	0 (0)	0 (0)	0 (0)	0.99
Catheter-related bloodstream infections	0 (0)	0 (0)	0 (0)	0.99
Thrombocytopenia	15 (33)	7 (26)	8 (44)	0.20
Neurologic complications	1 (2)	0 (0)	1 (6)	0.40

All statistically significant (**p**-value < 0.05) results appear in bold

Number of adverse events per session, n (%)

$ECCO_2R$: extracorporeal carbon dioxide removal. $ECCO_2R$-related adverse events' definitions are given in the Supplemental appendix

Discussion

In acute respiratory failure ICU patients, ultra-low volume ventilation (≤ 3 ml/kg PBW) was feasible for at least 12 h in 18 out of 45 sessions (40.0%) of $ECCO_2R$ sessions (confidence interval 25.3–54.6%). Higher blood flow rates were significantly associated with the success of ventilation with tidal volume ≤ 3 ml/kg PBW. Ventilation with Vt ≤ 3 ml/kg PBW was significantly associated with a greater reduction of driving pressure and lower mechanical power compared to the failure group.

Veno-venous $ECCO_2R$ devices form a broad heterogeneous group. They are classically divided into low blood flow and high blood flow $ECCO_2R$ devices [22]. Regarding clinical data, two main indications have fueled clinical studies: acute hypoxemic respiratory failure and acute decompensation of chronic obstructive pulmonary disease (COPD) [23, 24]. Three studies with relatively small number of patients succeeded in implementing ultra-protective ventilation facilitated by low flow veno-venous $ECCO_2R$ devices. In these studies, Vt was reduced to approximatively 4 ml/kg PBW (from 3.9 to 4.29) [12, 25, 26]. Neither hypercapnic acidosis nor major adverse events occurred. The SUPERNOVA pilot study was the first study that included low and high blood flow $ECCO_2R$ devices. It was a feasibility and safety study that included 95 patients with moderate ARDS [21]. The main endpoint was the proportion of patients who achieved ultra-protective ventilation (4 ml/kg PBW) by 8 h after the start of $ECCO_2R$ (78%; 95% confidence interval 68–89%). Two randomized controlled studies tried to lower the Vt less or equal than 3 ml/kg PBW. The first one (XTRAVENT study) used an arterio-venous $ECCO_2R$ device, which is seldom used nowadays, and patients never reached a tidal volume of 3 ml/kg in the $ECCO_2R$ group [27]. The second one is a recent large randomized controlled trial which included 412 moderate to severe ARDS patients and used low blood flow $ECCO_2R$ devices (REST study) [16]. Again, the $ECCO_2R$ group failed to achieve the 3 ml/kg PBW objective for Vt and there was no difference in the primary outcome (90-day mortality). On day 2 post randomization the reduction in Vt from the baseline was modest, dropping from 6.3 to 4.5 ml/kg PBW. Moreover, this reduction was paired with an increase in respiratory rate and in $PaCO_2$ which could be explained by an insufficient CO_2 removal by the $ECCO_2R$ device used.

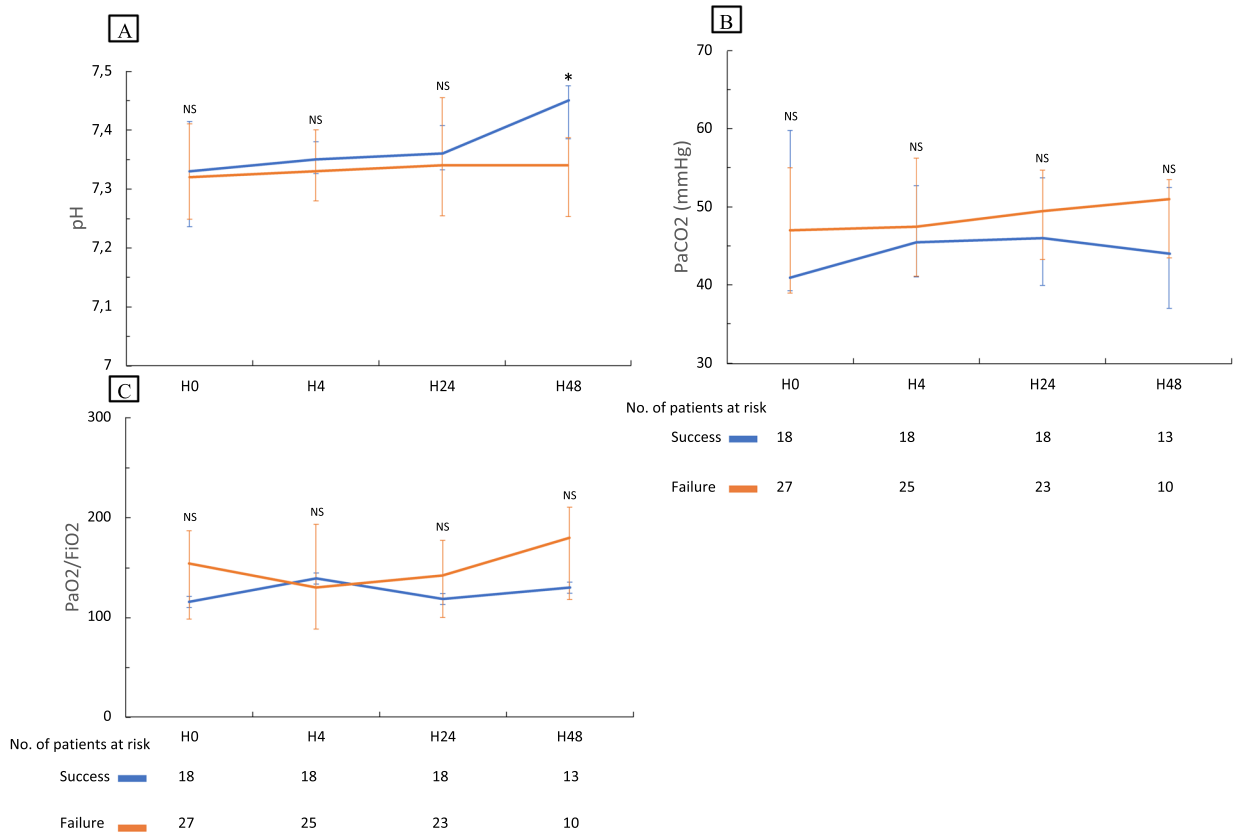

Fig. 2 Evolution over time of gas exchanges. Median, 1st and 3rd quartiles values of pH (**A**), partial pressure of arterial CO_2 ($PaCO_2$) (**B**), ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) (C) at the start of $ECCO_2R$ (H0), 4, 24, 48 h after initiation of $ECCO_2R$ in the failure group (> 3 ml/kg of predicted body weight) and in the success group (≤ 3 ml/kg of predicted body weight). *$p < 0.05$ between groups, NS: not significant

Feasibility

We successfully reached a tidal volume less or equal to 3 ml/kg PBW at 24 h of the start of ECCO2R in 18 out of 45 sessions (40.0%) sessions. The main factor associated with success was blood flow rates (adjusted OR per 100 ml/min increase 1.51 (95%CI 1.21–1.90, $p = 0.0003$). The median tidal volume was 2.1 ml/kg PBW in the success group at 24 h. To our knowledge, no study reports such low tidal volumes with $ECCO_2R$ devices. Previous studies with $ECCO_2R$ did not reach comparable Vt, either because there were not designed to or because they failed to achieve the Vt ≤ 3 ml/kg PBW objective. The main plausible cause for this failure when studying previous reports is insufficient CO_2 removal. Decarboxylation depends on extracorporeal blood flow and gas flow when considering similar gas exchangers and $PaCO_2$ [28]. The decarboxylation index was recently described (product of extracorporeal blood flow and gas flow) and found to be linearly associated with extracorporeal CO_2 removal. The authors also report that significant extracorporeal blood flow values must be used in order to obtain an effective decarboxylation index and clinically relevant CO_2 removal [29]. Combes et al. performed a secondary analysis of the SUPERNOVA trial and found that Vt of 4 ml/kg have been obtained more frequently and with a lower rate of adverse events by devices with higher CO_2 extraction (membrane area of 1.30 m^2; blood flow between 800 and 1000 ml/min)[30]. Our results support these findings.

Efficiency

While Vt was reduced, driving pressure was also significantly decreased. Variation of driving pressure at 24 h in the success group (from 20 [16–23] to 9.5 [5–13], $p < 0.001$) cmH_2O) was superior to that of the failure group. Comparatively, in the REST trial, driving pressure was decreased from 14.9 to 11.1 cmH_2O in the $ECCO_2R$ group. In an additional analysis (supplementary Fig. 2), we found a correlation between decrease of Vt and decrease of driving pressure only in the high blood flow rate group. Mechanical power, which reflects all the components potentially associated with VILI (airway

pressures (Pplat, PEEP), volume (Vt), flow and respiratory rate [19]) was significantly lower in the success group at 24 h (Supplementary Fig. 1 and Supplementary Table 4). Finally, despite the significant decrease in Vt and respiratory rate, pH and $PaCO_2$ stayed within physiological ranges, and no hypercapnic acidosis occurred, respiratory rate was even lower at 24 h in the success group (See Supplementary Tables 1-2-3).

Safety

In the overall population, thrombocytopenia was the most frequent adverse event (33.3% of all sessions). However, compared to previously published studies on $ECCO_2R$, our cohort included patients with multiple risks of thrombocytopenia such as cirrhosis, sepsis, surgery, acute gastrointestinal bleeding. These patients are usually excluded from $ECCO_2R$ studies (Supplementary Table 5). No significant worsening of hypoxemia related to the implementation of $ECCO_2R$ and low tidal volumes was recorded, as it has been reported in other studies [31]. The success group was not associated with more adverse events than the failure group. Circuit or membrane coagulation happened in 7 sessions (15.6%) in the failure group, 5 events during sessions with anticoagulation and 2 events during sessions without anticoagulation.

Limits

This study bears some obvious limits inherent to its retrospective methodology. The decision to start ultraprotective ventilation facilitated by $ECCO_2R$ was made as a team including clinicians in charge of the patient. Moreover, when this decision was reached, the choice of the $ECCO_2R$ device and its resulting consequences (cannula size, blood flow rate) were not randomized but left to clinicians' decision. Consequently, the two groups display a difference in driving pressure at baseline as well as PaO_2/FiO_2 (although not significant). One hypothesis is that high flow $ECCO_2R$ devices were spontaneously the preferred approach, by the clinicians in charge, in more severe patients. Because of this difference, we can only speculate on the effect of high blood flow devices on tidal volume in patients with high compliance and low driving pressure. Indeed, in our cohort, patients with high compliance and low driving pressure before $ECCO_2R$ start were mostly treated with low blood flow devices. Low survival rates in our cohort could be explained by the severity of our patients at admission. Indeed, overall SAPS II score was 52 [36–62] and SOFA score was 10 [7–13]. Both these scores reflect high predicted ICU mortality [17, 18]. Patients in our cohort are usually excluded from other $ECCO_2R$-related studies: patients at high hemorrhagic risk, patients with cirrhosis (Child–Pugh Score $\geq$ B) or liver failure, patients under high doses of norepinephrine [27] (Supplementary Table 5). However, it should be noted that use made by the clinicians of the $ECCO_2R$ devices and of the ventilation strategies could impact outcomes of our patients, which implies caution in the decision to start these devices. Finally, we included all patients treated with $ECCO_2R$ in our ICU which may have limited homogeneity of our population and therefore limit interpretability of the results.

Future directions

Our results point to the importance of high blood flow rates to achieve ultra-low volume ventilation. Future $ECCO_2R$ related studies should differentiate low and high blood flow $ECCO_2R$ devices as they have different efficacy and objectives. This study was not designed to assess superiority of one type of device over the other. However, with our results we could help better design future trials as high blood flow $ECCO_2R$ devices seem to allow a lower Vt and driving pressure. Given the results of our study and previously published data, we could consider using high blood flow $ECCO_2R$ devices in future studies that would assess clinical benefits of ultra-low volume ventilation.

Conclusion

Ultra-low volume ventilation ($\leq$3 ml/kg PBW) was feasible, Higher blood flow rate was the main factor associated with the success of ultra-low volume ventilation. In future $ECCO_2R$-related studies, blood flow should be considered in order to achieve effective ultra-low volume ventilation.

Abbreviations

Vt	Tidal volume
$ECCO_2R$	Extra corporeal carbon dioxide removal
ICU	Intensive Care Unit
IQR	Inter quartile range
$PaCO_2$	Carbon dioxide partial pressure
PaO_2/FiO_2	Arterial to inspired O2 fraction ratio

Supplementary Information

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Supplementary Material 1

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Author contributions

CM had a major role in the acquisition of data as well as writing the manuscript. TR and AP had a major role in the acquisition of data. TR, YA, MC, CLB, JP, IL made substantial contributions to the writing of the manuscript. ADJ made substantial contributions to the conception of the work as well as contributions to the draft and revisions of the work. ADJ and NM had a major role in analysis of the data. YA, MC, JP, CLB, IL made substantial contributions to the

conception of the work and interpretation of data. SJ was a substantial contributor to designing the work as well as interpretation of the data. SJ revised the work in its entirety. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The institutional ethics committee reviewed the retrospective use of anonymous data for scientific purpose and waived the need to obtain informed written consent. The Institutional Review Board (IRB) of Montpellier University Hospital approved the study (2019_IRB-MTP_05-25).

Consent for publication
Not applicable.

Competing interests
Pr Jaber reports receiving consulting fees from Drager, Medtronic, Mindray, Fresenius, Baxter, and Fisher & Paykel. Pr De Jong reports receiving remuneration for presentations from Medtronic, Drager and Fisher & Paykel. Dr Monet reports receiving remuneration for presentations from Medtronic. The other authors declare that they have no competing interests.

Author details
[1]Department of Anesthesia and Intensive Care Unit, Regional University Hospital of Montpellier, St-Eloi Hospital, PhyMedExp, INSERM U1046, CNRS UMR, University of Montpellier, 9214 Montpellier Cedex 5, France. [2]PhyMedExp, INSERM U1046, CNRS UMR, University of Montpellier, 9214 Montpellier, France. [3]Medical Information, IMAG, CNRS, Centre Hospitalier Regional Universitaire de Montpellier, Univ Montpellier, Montpellier, France. [4]Département d'informatique Médicale, CHRU Montpellier, Institut Desbrest de Santé Publique (IDESP) INSERM, Université de Montpellier, Montpellier, France.

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